

REMARKS UNDER 37 CFR §1.116

Applicants acknowledge the current status of the claims as reported in the Office Action mailed 11 August 2005. Claims 4-12 and 14-61 are currently pending in this application, claims 37 and 38 are allowed, claims 39-43 and 47-60 are withdrawn from consideration, and claims 4-12, 14-36, 44-46 and 61 are under consideration. Reconsideration and allowance of the application in light of the foregoing amendments and the following remarks are respectfully requested.

Applicants thank the Examiner for the courtesy of Examiner's interview, conducted on 16 November 2005 to discuss the bases of the outstanding rejections to Applicants' application. This interview forms the basis for the present remarks.

Claim 4 is hereby canceled without prejudice to advance examination of the present application to allowance. Applicants reserve the right to prosecute canceled subject matter in a later-filed continuation application, which properly claims the benefit of this application.

Claim 5 is amended such that it is an independent claim. Claims 6-10 are amended to depend from claim 5. Support for these amendments can be found throughout the specification as filed, and in the claims as filed. No new matter is added.

Claims 16-21 are amended by inserting the term "-- said epitope of --" just after the term "-- dissociates from--" such that the claims are directed to an isolated antibody, or antigen-binding portion thereof, that binds to an epitope of human IL-18 and dissociates from said epitope with the respective recited  $k_{off}$  rate constant. These amendments are made without prejudice to more precisely recite Applicants' invention. Applicants assert these amendments are made for reasons unrelated to patentability, for the purpose of style, grammatical structure, and readability of the claims. These amendments do not alter the scope or breadth of the claims or add new matter.

Claim 44 is amended such that the pharmaceutical composition comprises an antibody, or antigen-binding portion thereof, of any of claims 5-12 and 14-38, and a pharmaceutically acceptable carrier. Support for these amendments can be found throughout the specification as filed, and in the claims as filed. No new matter is added.

Reconsideration and allowance of the pending claims in light of the foregoing amendments and the following remarks are respectfully requested.

**Withdrawal of Objections and Rejections**

Applicants acknowledge the withdrawal of the previous rejection of claim 44 as being dependent upon a canceled claim.

**Claim rejections under 35 USC §112 first paragraph**

In the Office Action, at page 2, paragraph 6, claims 22, 29, 36 and their dependent claims 23-28, 32-35 and 44-46 are rejected under 35 USC §112, first paragraph, as containing subject matter not described in such a way as to convey to one skilled in the art that the Applicant was in possession of the claimed invention. Specifically, the Examiner asserts that Applicants have disclosed single chain antibodies comprising one variable region from light chain and one variable region from heavy chain but have not disclosed antibodies which comprise two heavy or two light chain variable regions. Applicants respectfully disagree.

In the specification as filed, on page 12, lines 4-28, Applicants teach and disclose examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) *Nature* 341:544-546 ), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR).

Applicants assert that antigen binding fragments with two heavy or two light chains are well known in the art (Ward et al., (1989) *Nature* 341:544-546). Applicants have previously provided a copy of the disclosure of Ward et al., to the examiner, wherein Ward et al disclose that isolated VH domains, can and do bind antigen with high affinities. Applicants, therefore, submit that antibodies and antigen-binding fragments comprising two heavy or two light chain variable domains capable of binding an antigen with high affinities are known in the art, and Applicants' specification as filed fully enables such human antibodies and antigen binding portions thereof, which are capable of binding human IL-18.

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejection of claims 22, 29, 36 and their dependent claims 23-28, 32-35 and 44-46 under 35 USC §112 first paragraph.

In the Office Action, at page 3, paragraph 3, claims 22-36 and the dependent claims 39-46 are rejected under 35 USC §112, first paragraph, as containing subject matter not described in such a way as to convey to one skilled in the art that the Applicant was in possession of the claimed invention. Specifically, the Examiner continues to assert that the specification, while being enabling for antibodies

and antigen-binding fragments thereof, in which the three CDR's in the heavy chain variable region or the three CDR's in the light chain variable region are all defined by a single antibody, and which bind the relevant antigen (human IL-18 or a peptide epitope thereof), and for mutants of these antibodies in which a limited number of defined changes are made in one or more CDRs; does not reasonably provide enablement for antibodies and antigen-binding fragments thereof that comprise less than three heavy chain CDRs or three light chain CDRs defined by the amino acid sequence of a parental antibody that binds the same antigen. Specifically, the Examiner continues to point to claims 30 and 31 which recite a light chain variable region having an amino acid sequence of SEQ ID NO:15 and asserts that the specific sequence represents only a small portion, but not three CDR's of a light chain. Applicants respectfully disagree and traverse the rejection.

Independent claims 22, 29 and 36 comprise "at least two variable regions". For reasons stated in the response to office action dated 9 August 2004, filed on 9 February 2005, Applicants have sufficiently described an antibody, or antigen-binding portion thereof comprising "at least two variable regions" and disclosed two examples of such antibodies capable of binding IL-18 (see page 28, lines 15-36). As is well known in the art, and as defined in the specification as filed, each variable region, a variable light (VL) region or a variable heavy (VH) region is composed of three CDRs (see page 11 line 29 to page 12, line 5). Applicants' invention comprises "at least two variable regions". It being well known in the art that each variable region comprises 3 CDRs, Applicants' claimed antibody necessarily comprises at least 6 CDRs. Therefore, antibodies or antigen-binding portions thereof of claims 22, 29 and 36 comprising "at least two variable regions" necessarily comprise six CDRs (three per variable region).

As stated previously claims 30 and 31 comprise a light chain variable region and a heavy chain variable region wherein each variable chain further comprises a CDR with a specific amino acid sequence. By definition, each variable region is composed of three CDRs (see page 12, lines 3-5). Claims 30 and 31 further specify that the recited light chain variable region (LCVR) comprises amino acid sequence of SEQ ID NO:15, and the recited heavy chain variable region (HCVR) comprises amino acid sequence of SEQ ID NO:16 and 17 respectively. SEQ ID NO:15 recites a feature of the recited LCVR element. SEQ ID NO:15 does not define the three CDRs of the recited LCVR. Applicants have defined a variable region as composed of three CDRs. Therefore in claims 30 and 31 the term "having" should be interpreted as comprising, and not consisting of one specific CDR sequence.

Antibodies of claims 22-36 comprise six CDRs. Further claims 25-36 recite specific sequences. Applicants teach how to generate, screen and identify antibodies capable of binding human IL-18 (See Example 1-4, pages 28-36 of the specification as filed). From Applicant's disclosure, one of ordinary skill in the art can readily comprehend the structural features necessary to generate antibodies to IL-18. Accordingly, Applicants submit that one skilled in the art would recognize that Applicants, at the time of

filling, were in possession of the claimed invention and that the specification as filed fully enables one skilled in the art.

In view of the foregoing amendments and remarks, Applicants respectfully request the removal of the rejection of claims 22-36 and 39-46 under 35 USC §112, first paragraph .

**Claim rejections under 35 USC §103(a)**

In the Office Action, at page 5, paragraph 8, claims 4-12, 14-24, 44-46 and 61 are again rejected under 35 USC §103(a) as being unpatentable over Kucherlapati et al., (US Patent No. 6,075,181) and Dinarello et al., (J. Leukoc. Biol. 1998; 63:658-664). Examiner asserts that the combination of Dinarello et al. and Kucherlapati et al. provide both the motivation to produce human antibodies to human IL-18. Applicants respectfully disagree.

For purposes of advancing examination of the present application to allowance only, Applicants have canceled claim 4 without waiver or prejudice. Applicants reserve the right to prosecute canceled subject matter in a later-filed continuation application, which properly claims the benefit of this application. Claim 5 is amended such that it is an independent claim. Claims 6-10 are amended to depend from claim 5. Claim 44 is amended such that the pharmaceutical composition comprises an antibody, or antigen-binding portion thereof, of any of claims 5-12 and 14-38, and a pharmaceutically acceptable carrier. Support for these amendments can be found throughout the specification as filed, and in the claims as filed. No new matter is added.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all claim limitations. Second, there must be a reasonable expectation of success. Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. (see generally MPEP § 2143).

Hindsight reconstruction of a claimed invention, absent a teaching or suggestion in the art is impermissible. (MPEP § 2142).

Applicant's invention is directed to human antibodies or antigen binding portions thereof capable of binding human IL-18. Specifically, the claims as amended, are directed to human antibodies or antigen binding portions thereof capable of binding human IL-18 with specific binding characteristics defined by  $k_{off}$  rate constants or specific inhibitory characteristics defined by IC<sub>50</sub> values.

Dinarello et al. disclose recombinant human IL-18. The cited art identifies IL-18 as a potential therapeutic target, and discloses possible "therapeutic options for specific blockade of IL-18: neutralizing

anti-18 antibodies, soluble receptors to IL-18, and non-agonistic antibodies that bind either the ligand binding IL-18R or the IL-1Rrp." Dinerello et al. do not teach, suggest or motivate one skilled in the art to generate fully human antibodies to human IL-18 with specific binding characteristics with respect to the antigen defined by  $k_{off}$  rate constants or specific inhibitory characteristics defined by IC<sub>50</sub> values.

Kucherlapati et al. disclose a method of generating fully human antibodies to antigens.

Kucherlapati et al. do not disclose human IL-18 as an antigen. Kucherlapati et al. do not disclose IL-18, generally, as an antigen. Finally, Kucherlapati et al. do not teach, suggest or motivate one skilled in the art to generate a fully human antibody to either IL-18, or specifically to human IL-18 with specific binding characteristics with respect to the antigen defined by  $k_{off}$  rate constants or specific inhibitory characteristics defined by IC<sub>50</sub> values.

Applicants assert that the above-cited references, either singularly or in combination, do not teach, suggest, or motivate one skilled in the art, Applicants' human anti-IL-18 antibodies or method of making the same. In addition, Applicants reiterate that the Examiner fails to provide any evidence (absent Applicants' present disclosure) to support motivation to combine the cited art, as required to establish a *prima facie* case of obviousness, in the reconstruction of Applicants' claimed invention.

It is well established in case law that to establish obviousness by combining or modifying the teachings of the prior art to produce the claimed invention there must be "substantial evidence", for a motivation to combine the cited art. *In Re Dembicza*k, 175 F.3d 994, Fed. Cir. 1999 and *In re Beasley*, (Serial No. 07/636,839), 2004 U.S. App LEXIS 25055, decided December 7, 2004. In *In re Dembicza*k, 175 F.3d 994, 999 (1999), the court stated that "evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, although "the suggestion more often comes from the teachings of the pertinent references." The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." Applicants' also draw the Examiner's attention to a recent decision of the U.S. Court of Appeals for the Federal Circuit, *In re Beasley*, (Serial No. 07/636,839), 2004 U.S. App LEXIS 25055, decided December 7, 2004. Not citable as precedent, this case is particularly instructive concerning the substantial evidence requirement for motivation to combine references.

Merely showing that all the elements of the claimed invention are known in the art is insufficient to establish obviousness. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir.

2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); “[t]he prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.” *In re O'Farrell*, 853 F.2d 894, 901 (1988); “It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor.” *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934 (1990); prior art must offer “suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art.” *In re Vaeck*, 947 F.2d 488, 496 (1991); “Knowledge in the prior art of every element of a patent claim, however, is not of itself sufficient to render claim obvious. The issue is whether substantial evidence supports the judgment (under the clear and convincing evidence standard) that a person having ordinary skill in the art would not have been motivated to replace the developing fluid/sample solution combination of Deutsch with flow provided solely by sample fluid.” *Abbott Labs. v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, 1358 (2003). Broad conclusory statements regarding the teaching of multiple references, standing alone, are not ‘evidence’.” (*In Re Dembicza*k, 175 F.3d 994, 1000 Fed. Cir. 1999).

In the present rejection to Applicants' claimed invention, the Examiner asserts that one of ordinary skill in the art would have been reasonably expected to combine the teaching of Dinarello et al. with those of Kucherlapati et al. to produce Applicants' antibodies. The Examiner has provided one reference (Dinarello et al.) that discloses IL-18 as a potential therapeutic target, and a “wish list” of “therapeutic options” including neutralizing antibodies. The Examiner then provides a second reference (Kucherlapati et al.) that discloses a method of making a fully human antibody. Without Applicants' disclosure, it is not obvious to one skilled in the art to make a leap from various therapeutic options as clinical strategy to block IL-18 to one specific cure, namely a human anti-IL-18 antibody. The Examiner makes the broad conclusory statement that even though neither reference teaches explicitly a human monoclonal antibody to human IL-18 it would be obvious to one of ordinary skill in the art to combine the teaching of Dinerello et al. and Kucherlapati to arrive at Applicants' invention. In *In re Kotzab*, 217 F.3d 1365, 1371(Fed. Cir. 2000), the court held that although the invention was a “technologically simple concept”, where “there was no finding as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of Kotzab's invention to make the combination in the manner claimed” the Board failed to make a proper case of *prima facie* obviousness. Unlike *Kotzab*, Applicants' invention is not “technologically simple.” Like *Kotzab*, without Applicants' disclosure it is not obvious to the skilled artisan to combine the teaching of Dinerello et al. and

Kucherlapati et al to arrive at Applicants' invention. The Examiner has failed to provide evidence of a suggestion, teaching, or motivation in the cited art to combine them and arrive at Applicants' invention.

In Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc. 381 F.3d 1371,1377 (2004), the court held that the invention, a combination of known methods to arrive at a separate treatment of arrhythmias, was non-obvious, because the mere "Recognition of the problem of treating complex heart arrhythmias does not render obvious the eventual solution. Recognition of a need does not render obvious the achievement that meets that need. There is an important distinction between the general motivation to cure an uncured disease (for example, the disease of multiple forms of heart irregularity), and the motivation to create a particular cure."

Like Cardiac Pacemakers, the Dinerello et al disclosure of IL-18 as a potential target in inflammatory disease, at best, serves as recognition of a problem (i.e., IL-18 mediated disease), with no motivation to seek out, to investigate, or to explore the potential use of a fully human antibody to human IL-18 as a solution. Kucherlapati et al. do not provide any motivation to create a particular cure or suggest IL-18 as an antigen (much less human IL-18). None of the cited art, singularly or in combination, provides any teaching, suggestion or motivation to arrive at Applicants' invention of a specific cure, a human anti-IL-18 antibody to human IL-18.

Applicants assert that, like the Board in Dembiczkak, the Examiner has combined one reference (Dinarello et al.) that discloses IL-18 as a potential therapeutic target, and a "wish list" of "therapeutic options" including neutralizing antibodies with a second reference (Kucherlapati et al.) that discloses a method of making a fully human antibody, analyzed them limitation-by-limitation without demonstrating how and where the references teach, suggest, or motivate that they should be or could be combined to arrive at Applicants' invention. A disclosure of a method to generate human monoclonal antibodies, combined with a reference disclosing neutralizing anti-IL-18 antibodies is not a clear and particular teaching, suggestion, or motivation to one of skill in the art to make the fully human anti-IL-18 antibody of the present invention. Applicants maintain that neither Kucherlapati nor Dinarello et al., singularly or in combination, teach or suggest making human antibodies to human IL-18 or further human antibodies to human IL-18 with specific binding characteristics. In fact, Applicants assert that, in view of the stated potential role of IL-18 as a therapeutic target, the fact that neither reference teach or suggest a fully human anti-human IL-18 monoclonal antibody is evidence (by its absence) that such an approach is novel, unobvious, and even unobvious-to-try (even to the principal investigators of the cited art, much less a person of ordinary skill in the art) at the time of filing the present invention.

In conclusion, Applicants assert that the Examiner fails to provide the requisite "*clear and particular showing*" of any suggestion or motivation to combine the cited references. The combination of the cited art is made by the Examiner, upon guidance, direction, and motivation to do so, by

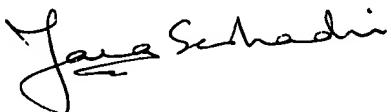
Applicants' present invention. This is hindsight reconstruction and is impermissible as a basis for rejection under 35 USC §103. (see MPEP § 2142). Applicants disagree with the Examiner's assertion that it is to combine the references, and respectfully request that the Examiner to withdraw the rejection.

Because the cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 4-12, 14-24, 44-46 and 61 as obvious under 35 USC §103(a). In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejection of claims 4-12, 14-24, 44-46 and 61 under 35 USC §103(a).

**Conclusion**

In view of the foregoing amendments and remarks, Applicants believe the rejections set forth in the Office Action dated 11 August 2005 have been avoided or overcome and consequently their application is in condition for allowance. Applicants, therefore, respectfully request reconsideration and removal of the rejections, and allowance of the pending claims as amended.

Respectfully submitted,



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